AWARD NUMBER: W81XWH-15-1-0705

TITLE: Beta Blockers for the Prevention of Acute Exacerbations of COPD

PRINCIPAL INVESTIGATOR: Mark T. Dransfield, MD

CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, AL 35294

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	30 Sept 2016 – 29 Sept 2017

4. TITLE AND SUBTITLE
Beta Blockers for the Prevention of Acute Exacerbations of COPD

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0705

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We are conducting a multicenter, randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate and severity of COPD exacerbations. The trial will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Major activities for this reporting period have centered on recruiting and enrollment at clinical sites, launching recruitment advertising campaigns locally and utilizing the COPD Foundation, and the addition of new clinical sites to remediate recruitment lag including regulatory approvals, training, and site initiation. The monthly enrollment goal is 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Some sites have met and exceeded this goal overall while others are underperforming. At the time of this report 242 subjects have been randomized. At the next DSMB meeting in November 2017 we will initiate discussions regarding site performance and possible site closeouts to allow redistribution of funds to high performing centers or additional new centers beyond those already planned.

15. SUBJECT TERMS
beta blockers , cardiovascular disease, COPD, exacerbation , metoprolol succinate, placebo-controlled, randomized

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	19	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION:

A substantial majority of chronic obstructive pulmonary disease (COPD)-related morbidity, mortality and healthcare costs are due to acute exacerbations, but existing medications have only a modest effect on reducing their frequency, even when used in combination. Observational studies suggest β-blockers may reduce the risk of COPD exacerbations; thus, we are conducting a randomized, placebo-controlled trial to definitively assess the impact of metoprolol succinate on the rate of COPD exacerbations. This is a multicenter, placebo-controlled, double-blind, prospective randomized trial that will enroll 1028 patients with at least moderately severe COPD over a 3-year period. Participants with at least moderate COPD will be randomized in a 1:1 fashion to receive metoprolol or placebo; the cohort will be enriched for patients at high risk for exacerbations. Patients will be screened and then randomized over a 2-week period and will then undergo a dose titration period for the following 6 weeks. Thereafter, patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4-week washout period. The primary endpoint is time to first occurrence of an acute exacerbation during the treatment period. Secondary end points include rates and severity of COPD exacerbations; rate of major cardiovascular events (MACE); all-cause mortality; lung function (forced expiratory volume in 1 s (FEV1)); dyspnea; quality of life; exercise capacity; markers of cardiac stretch (pro-NT brain natriuretic peptide) and systemic inflammation (high-sensitivity C reactive protein and fibrinogen). Analyses will be performed on an intent-to-treat basis.

KEYWORDS:
beta blockers
cardiovascular disease
COPD
exacerbation
metoprolol succinate
placebo-controlled
randomized

ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims to be achieved through the conduct of the proposed clinical trial:
Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.
Secondary: To estimate the effect of metoprolol succinate compared with placebo on the rate and severity of COPD exacerbations over 12 months, major adverse cardiac events (MACE), combined exacerbations and MACE, incidence and severity of metoprolol-related side effects including those that require cessation of drug, lung function, dyspnea, quality of life, exercise tolerance, hospitalization rates, and all-cause mortality.

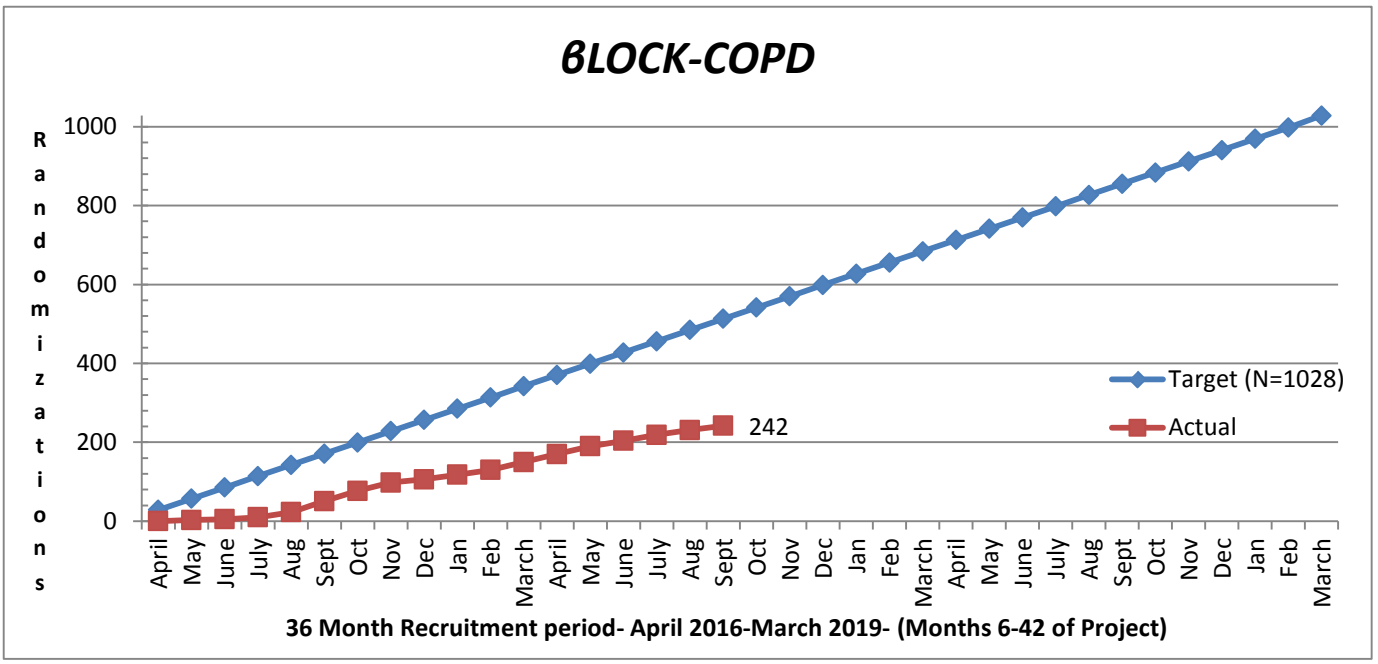
What was accomplished under these goals?

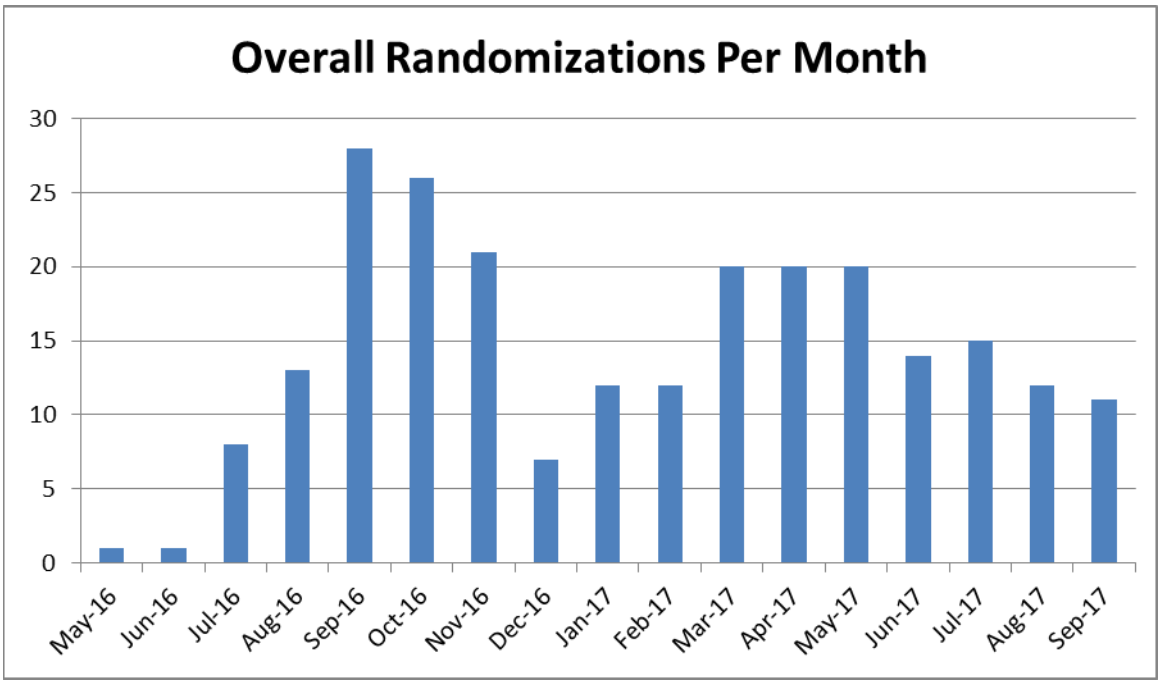
Major activities for this reporting period have centered on recruiting and enrollment at clinical sites, launching advertising campaigns locally and utilizing the COPD Foundation, and the addition of clinical sites to remediate recruitment lag including regulatory approvals, training, and site initiation and enrollment at new clinical sites. The original monthly enrollment goal was 28.5 across all sites, with each site enrolling an average of 2-3 participants per month. Some sites have met and/or exceeded this goal but others are underperforming. At the next DSMB

meeting in November 2017 we will initiate discussions regarding site performance and possible site closeouts to allow redistribution of funds to high performing centers or additional new centers. We have added 2 new centers in the last 12 months (LSU and Cleveland Clinic) and anticipate adding up to 8 additional centers in the next year.

Screen 4-6 subjects/month	6-42 months	Screening has started at all initiated sites
Randomize 2-3 subjects per site /month	6-42 months	The first subject was randomized in May 2016, two months later than anticipated based on delays in regulatory approvals. Since that time enrollment has been steadily increasing over all sites. See enrollment graphs below.
Complete study visits for 1 year + 1 month washout following enrolment	6-55 months	Ongoing
Data entry	6-55 months	No issues
Issue queries	6-56 months	No issues
Resolve queries	6-56 months	No issues
Adverse event assessment and reporting	6-55 months	No issues
Maintain IRB approval	6-60 months	Ongoing
Develop reports for DSMB	6-60 months	DSMB meetings have been held on 2DEC 2016 and 25 MAY 2017 and is being scheduled for NOV 2017. The DCC has developed reports as necessary.
Conduct monthly coordinator calls	6-56 months	Calls have been conduct monthly since August 2016. Weekly, biweekly to monthly calls have been conducted with PIs and other study staff since April 2016
Provide drug and placebo as needed to sites	6-55 months	Ongoing
Return unused drug and placebo to DPMD	56-58 months	N/A

Overall Randomizations April 2016 – September 2017

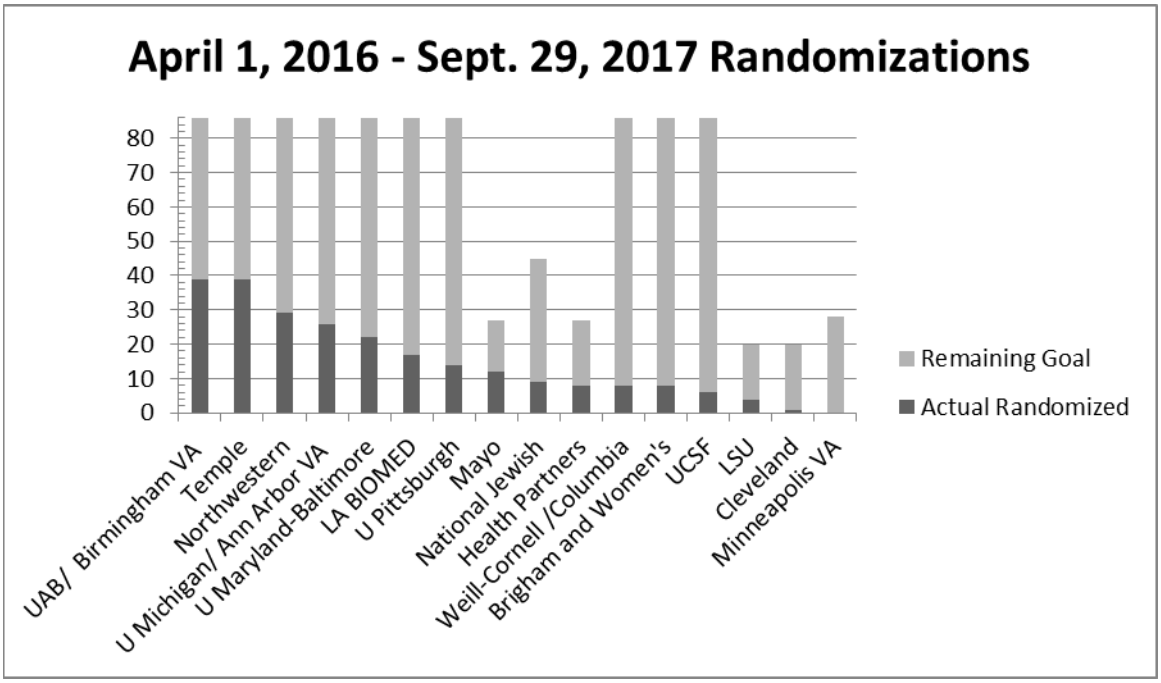




Actual Randomizations by site as of September 29, 2017

UAB/ Birmingham	
VA	39
Temple	39
Northwestern	29
U Michigan/ Ann Arbor VA	26
U Maryland-Baltimore	22
LA BIOMED	17
U Pittsburgh	14

Mayo	**12**
National Jewish	**9**
Health Partners	**8**
UCSF	**6**
Weill-Cornell /Columbia	**8**
Brigham and Women's	**8**
LSU	**4**
Minneapolis VA	**0**
Cleveland	**1**
TOTAL	**242**



What opportunities for training and professional development has the project provided?

Numerous pulmonary fellows and junior faculty have been involved in the study across sites providing experience and education regarding clinical trial execution.

How were the results disseminated to communities of interest?

During the first reporting period the following article was published: β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. PMID: 27267111.

Nothing to report during second reporting period. Efforts have focused on recruitment, enrollment, and additional clinical sites.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period clinical sites will continue recruitment and enrollment efforts and additional clinical sites will be initiated.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

CHANGES/PROBLEMS:

Changes in approach and reasons for change

While there have not been any reported problems related to ECG acquisition, the DSMC has recommended after its May25, 2017 meeting the implementation of central training (i.e., webcast training) for proper ECG acquisition. This training was provided to all applicable study staff on August 2017.

Furthermore, when we started the study we wanted to be conservative about enrolling patients at risk for bradycardia and thus chose a baseline heart rate of 70 as the lowest allowed for eligibility. We have not encountered any significant issues with bradycardia with this threshold and no patients have been taken off study drug for this reason. However, we have excluded a number of otherwise eligible patients and would therefore we have modified the protocol to lower the baseline heart rate requirement from 70 to 65. The Independent Research Monitor and members of the DSMC, including the cardiologist reviewed this change and were in agreement that this change is reasonable and raises no additional concerns from their perspective.

We also revised the protocol to make clarifications regarding dose adjustment. Investigators are to be handling dose titration based on his/her clinical judgment after consideration of vital signs, pulmonary function tests, and possible drug side effects along with the dose titration table.

These revisions were reviewed and approved by the UAB IRB and have also been disseminated to and IRB approved at all clinical sites. The revisions do not meet DOD HRPOs threshold for substantive amendments, and therefore no further action was required from DOD HRPO regarding the revisions.

Actual or anticipated problems or delays and actions or plans to resolve them

There was a slightly slower than expected start-up due to delays in regulatory approvals at the clinical sites. We have also experienced a lag in recruitment and enrollment and in order to address this have received approval to realign funds to accommodate the addition of new sites in order to meet the enrollment target. This realignment is critical in meeting the target within the prescribed time frame. Given the current study-wide enrollment rate (approximately 13 in

months July, August and September) there will be a shortfall of up to 552 subjects at the end of the originally planned enrollment period at month 42. At that point, approximately 476 (46%) of the required 1028 subjects will have been randomized. While enrollment at many current clinical sites is excellent, and improving at others, it is necessary to proactively develop solutions to deal with any shortfall.

The proposal to establish additional sub-contracts with up to ten additional clinical sites in order more efficiently reach the targeted enrollment is necessary. Each new site will be contracted to recruit, enroll, and randomize up to 20 subjects over years 3 and 4 of the project shortfall. These enrollment and budgeting adjustments will be made within the current budget award amount by utilizing funds that were originally budgeted for the University of Colorado before they were replaced at a lower budgeted amount by National Jewish Health, by offering a budget that consists of a reduced per patient capitated payment to the new sub-contracts, and by reducing the amount budgeted for capitated per patient payments for existing subcontracts in years 3 and 4 based on actual enrollment performance in year 2. This process has begun.

The Minnesota VA has had ongoing issues with privacy requirements and the DCC's websites and staffing. These issue have recently been resolved and they anticipate screening and enrollment will begin soon at their site.

Changes that had a significant impact on expenditures

Because of the lower than expected subject recruitment in year 1 we amended the subcontracts for each site to allow for the use of remaining year 1 funds during year 2. We plan to utilize this strategy again when issuing year 3 subcontracts, however, we will also be reducing the amount budgeted for capitated per patient payments for existing subcontracts in years 3 and 4 based on actual enrollment performance in year 2 to allow for additional sites to be added without impacting the overall budget.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

During this second reporting period the Modification out lined below and discussed above has been made. These revisions have been reviewed and approved by the UAB IRB at all sites. The revisions do not meet DOD HRPOs threshold for substantive amendments, and therefore no further action was required from DOD HRPO regarding the revisions.

Protocol version 03 dated 24 FEB 2017.
When we started the study we wanted to be conservative about enrolling patients at risk for bradycardia and thus chose a baseline heart rate of 70 as the lowest allowed for eligibility. We have not encountered any significant issues with bradycardia with this threshold and no patients have been taken off study drug for this reason. However, we have excluded a number of otherwise eligible patients and would therefore like to lower the baseline heart rate requirement from 70 to 65. The Independent Research Monitor and members of the DSMC, including the cardiologist have review this change and are in agreement that this change is reasonable and raises no additional concerns from their perspective. We would also like to revise the protocol to make clarifications regarding dose adjustment. Investigators will be handling dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects along with the dose titration table.
Summary of protocol revisions:

Page 7 – Exclusion criteria #8 revised, “resting heart rate less than 70 beats per minute…” to “resting heart rate less than *65* beats per minute…”

Page 15 – Clinic Visit 2 Randomization #6 revised, “Only those with resting HR greater than or equal to70…” to “only those with resting HR greater than or equal to *65…”*

Page 15 – Clinic Visit 5 - #7 revised to, “For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on *assessment of symptoms and* tolerability according to the dose adjustment protocol (Table 3). *The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects.*

Page 16 – Dose Adjustment Protocol Table, Enrollment/Randomization HR has been lowered to >= *65.*

Page 17- clinic visit 8 revised to, “For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on *assessment of symptoms and* tolerability according to the dose adjustment protocol (Table 3). *The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects.*

Typos have been corrected throughout. The protocol version has been updated to v 03 and dated February 24, 2017.

The consent form was not changed as a result of the protocol revisions.

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

PRODUCTS:

Publications, conference papers, and presentations

First reporting period:

Journal publications

BMJ Open, vol. 6(6) pp. e012292

β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol.

Bhatt, SP; Connett, JE; Voelker, H; Lindberg, SM; Westfall, E; Wells, JM; Lazarus, SC; Criner, GJ; Dransfield, MT
PMID: 27267111
URL - http://www.ncbi.nlm.nih.gov/pubmed/27267111?dopt=Citation

acknowledgement of federal support – yes

Second Reporting period:

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

Nothing to report.

Website(s) or other Internet site(s)

First reporting period:

The trial has been listed on ClinicalTrials.gov. The NCT number is NCT02587351.

url: https://clinicaltrials.gov/

We have developed an informational website for participants and providers. This site provides a broad overview of the trial including contact information for UAB, the DCC, the research pharmacy and all clinicial sites.

url: http://blockcopd.org/

Second reporting period:

nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

First reporting period:

We have developed a separate protocol for the collections and storage of serum, plasma and whole blood samples. The protocol has been approved by the UAB IRB. We ask other interested clinical sites that have the internal resources available to participate in the specimen collection protocol as well.

Second Reporting period:

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

University of Alabama at Birmingham

Name: Mark T. Dransfield
Project Role: PI
Research Identifier: 0000-0003-0346-1956
Nearest Person Month worked: 2.4
Contribution to Project: Dr. Dransfield is the PI of the Project. He oversees protocol related activities at all research sites and is the local site PI at UAB.

Name: Elizabeth Westfall
Project Role: Program Director
Research Identifier: N/A
Nearest Person Month worked: 2.4

Contribution to Project: Ms. Westfall assists in the regulatory and financial administration of this grant. This includes initiating subcontracts and overseeing disbursement of payments to subaward sites as well as overseeing human subject approvals.

Minnesota DCC

Name: Dr. John Connett
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.8
Contribution to Project: Dr. Connett oversees the project at the DCC site. He supervises the day-to-day operation of the Data Coordinating Center. Dr. Connett oversees the development of data collection procedures and methods for data transmission and management.

Name: Helen Voelker
Project Role: Information Technologies Manager
Research Identifier: N/A
Nearest Person Month worked: 4.2
Contribution to Project: Ms. Voelker develops database schemas, edits, and updates procedures for study data. Ms. Voelker develops the distributed data entry and data transmission system.

Name: Sarah Lindberg
Project Role: Protocol Manager
Research Identifier: N/A
Nearest Person Month worked: 3.6
Contribution to Project: Ms. Lindberg assists with writing sections of the Manual of Procedures, designing study data forms, and analyzing data for Steering Committee and DSMB meeting.

Name: Irene Olson
Project Role: Data Quality Control
Research Identifier: N/A
Nearest Person Month worked: 3
Contribution to Project: Ms. Olson assists Ms. Voelker in creating schemas and databases for forms.

Temple University School of Pharmacy

Name: David Lebo
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 2.4
Contribution to Project: Dr. Lebo is the PI for the Temple Pharmacy site.
Dr. Lebo is responsible for producing, labeling, and distributing the study drug for this project. Mr. Lebo oversees the supply chain of the medication and monitors it for labeling and packaging deviations.

University of Michigan

Name: MeiLan Han
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Han is the PI for the University of Michigan site.
Dr. Han oversees day-to-day research activities at this site.

Name: Jeffrey Curtis
Project Role: Co-PI
Research Identifier: N/A
Nearest Person Month worked: .6
Contribution to Project: Dr. Curtis is the Co-PI for the University of Michigan site and the PI at the VAAAHS site. Mr. Curtis oversees day to day research activities at this site.

Weill Cornell Medical College

Name: Fernando Martinez
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .23
Contribution to Project: Dr. Martinez is the PI for the Weil Cornell Medical College site.
Dr. Martinez oversees day to day research activities at this site.

Weill Cornell Medical College

Name: Keith Brenner
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. Brenner is the Co-Investigator for the Weil Cornell Medical College subsite at Columbia University Dr. Brenner oversees day to day research activities at this site.

New York Presbyterian Queens (NYPQ)

Name: Anthony Smith
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked:
Contribution to Project: Dr. Smith is the PI at the New York Presbyterian Queens site. This is a subsite of Weill Cornell Medical College. Dr. Smith will oversee recruitment at this site.

New York Methodist (NYM)

Name: Jeremy Weingarten
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked:
Contribution to Project: Dr. Weingarten is the PI at the New York Methodist site. This is a subsite of Weill Cornell Medical College. Dr. Weingarten will oversee recruitment at this site.

University of Maryland

Name: Robert M. Reed
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Dr. Reed is the PI for the University of Maryland, Baltimore site. Dr. Reed oversees day to day research activities at this site.

Northwestern University

Name: Ravi Kalhan
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. Kalhan is the PI for the Northwestern University site. Dr. Kalhan oversees day to day research activities at this site.

Name: Sharon Rosenberg
Project Role: Co-PI
Research Identifier: N/A
Nearest Person Month worked: .18
Contribution to Project: Dr. Rosenberg is the Co-Investigator for the Northwestern University site. Dr. Rosenberg assists Dr. Kalhan with day to day research activities at this site and supervise in data analysis and preparation of manuscripts.

University of Pittsburgh

Name: Frank Sciurba
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .6

Contribution to Project: Dr. Sciurba is the PI for the University of Pittsburgh site. Dr. Sciurba oversees day to day research activities at this site.

Temple University

Name: Gerard Criner
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: ..60
Contribution to Project: Dr. Criner is the PI for the Temple University – Clinical site. Dr. Criner oversees day to day research activities at this site.

Name: Nathaniel Marchetti
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .24
Contribution to Project: Dr. Marchetti is the Co-Investigator for the Temple University – Clinical site. Dr. Marchetti assists Dr. Criner with day to day research activities at this site. In addition Dr. Marchetti assists with recruitment, enrollment, and retention.

Name: Dee Fehrle
Project Role: RN, Research Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.8
Contribution to Project: Dee Fehrle is the Research Nurse Coordinator at the Temple University – Clinical site. Dee manages day to day study activities at this site. Dee recruits and enrolls patients as well as see patients at each visit as outlined in the protocol. Dee also collects patient data.

Minneapolis VA

Name: Ken Kunisaki
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Kunisaki is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Kunisaki assists with protocol related activities at this site. He is also involved with data analysis and will contribute to the manuscript writing and presentation

Name: Christine Wendt
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .60
Contribution to Project: Dr. Wendt is the Co-Investigator for the Minnesota Veterans Research and Education Foundation site. Dr. Wendt assists Dr. Niewoehner with protocol related activities at this site.

Name: Susan Johnson
Project Role: Project Coordinator/ Data Analyst
Research Identifier: N/A
Nearest Person Month worked: 1.44
Contribution to Project: Susan is the Project Coordinator/ Data Analyst for the Minnesota Veterans Research and Education Foundation site. Susan is responsible for patient screening and data analysis throughout the study.

Mayo Clinic

Name: Paul Scanlon
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Scanlon is the PI for the Mayo Clinic site. Dr. Scanlon oversees day to day research activities at this site.

Brigham and Women's Hospital

Name: Carolyn Come
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.2
Contribution to Project: Dr. Come is the PI for the Brigham and Women's Hospital site. Dr. Come oversees the day to day research activities at this site.

Health Partners Institute

Name: Charlene McEvoy
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .36
Contribution to Project: Dr. McEvoy is the PI for the HealthPartners Institute site. Dr. McEvoy
Oversees the day to day research activities at this site.

Brigham and Women's Hospital

Name: Pam Neuenfeldt
Project Role: Project Manager
Research Identifier: N/A
Nearest Person Month worked: 2.55
Contribution to Project: Pam assists the PI with the day-to-day activities associated with this project. She is also responsible for the regulatory documentation at this site.

National Jewish Health

Name: Barry Make
Project Role: PI

Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Make is the PI for the National Jewish Health site. Dr. Make Oversees the day to day research activities at this site.

Los Angeles Biomedical Research Institute

Name: William Stringer
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .5
Contribution to Project: Dr. Stringer is the PI for the Los Angeles Biomedical Research Institute. Dr. Stringer oversees the day to day research activities at this site.

Los Angeles Biomedical Research Institute

Name: Richard Casaburi
Project Role: Co-Investigator
Research Identifier: N/A
Nearest Person Month worked: .3
Contribution to Project: Dr. Casaburi assists with the day to day research activities at this site and serve as a resource for this project. He will assists with data analysis and manuscript preparation.

University of San California, San Francisco

Name: Stephen Lazarus
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .53
Contribution to Project: Dr. Lazarus is the PI for UCSF. Dr. Lazarus is responsible for overall implementation and oversight of this project at the UCSF site.

University of San California, San Francisco

Name: Prescott Woodruff
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Woodruff is the Co-Investigator at UCSF. Dr. Woodruff assists Dr. Lazarus with the day to day research activities at this site.

Louisiana State University

Name: Matthew Lammi
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: 1.20
Contribution to Project: Dr. Lammi is the PI at the Louisiana State University site. He is responsible for the overall supervision and direction of the project at LSUHSC.

Louisiana State University

Name: Connie Romaine
Project Role: Clinical Research Nurse
Research Identifier: N/A
Nearest Person Month worked: 1.31
Contribution to Project: Connie screens potential participants and assists Dr. Lammi with data and sample collection, staff education, meetings and teleconferences.

Cleveland Clinic Foundation

Name: Umur Hatipoglu
Project Role: PI
Research Identifier: N/A
Nearest Person Month worked: .12
Contribution to Project: Dr. Hatipoglu is the PI at the Cleveland Clinic Foundation site. He is responsible for the overall supervision and direction of the project at Cleveland Clinic Foundation.

Cleveland Clinic Foundation

Name: Rick Rice
Project Role: Study Coordinator
Research Identifier: N/A
Nearest Person Month worked: 3.0
Contribution to Project: Rick is responsible for obtaining informed consent on all subjects enrolled. He is responsible for screening/enrolling participants as well as collect and enter data.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Ken Kunisaki, Co-Investigator at the Minneapolis VA took over as PI from Dennis E. Niewoehner, MD. This changed was reviewed and approved by DOD HRPO on September 21, 2017.

What other organizations were involved as partners?

Nothing to Report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: See attachment 1

APPENDICES:

Second reporting period: NONE.

PR140170: Beta Blockers for the Prevention of Acute Exacerbations of COPD

PI: Mark Dransfield, University of Alabama at Birmingham

Budget: $11,241,567 **Topic Area:** Respiratory Health **Mechanism:** Clinical Trial Award

Research Area: Chemoprevention, Chemotherapy **Award Status:** Open; 9/30/2015 - 9/29/2020

Study Goals:

Carry out a clinical trial to examine the potential role of beta-blockers in the treatment of chronic obstructive pulmonary disease (COPD).

Specific Aims:

(1) Determine the effect of once-daily metoprolol succinate, compared with placebo, on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and do not have absolute indications for beta-blocker therapy. (2) Estimate the effect of metoprolol succinate, compared with placebo, on the rate and severity of COPD exacerbations over 12 months, incidence and severity of metoprolol-related side effects, lung function, dyspnea, exercise tolerance, quality of life, hospitalization rates, rate of combined cardiovascular events (myocardial infarction, percutaneous coronary intervention, sudden death, stroke), and all-cause mortality.

Key Accomplishments:

- Ended September 2017 (18th month of the 36 month recruitment period) at 47% of projected target randomized.
- 2 additional clinical sites and subsites added to boost recruitment. Up to 8 more will be added in year 3.
- Advertising campaign launched in collaboration with the COPD Foundation.
- December 2, 2016 and May 25, 2017 the DSMC recommended the trial proceed according to the protocol.
- 19 subcontracts successfully executed including DCC, pharmacy, original clinical sites, and 3 add on clinical site.
- 17 clinical and clinical subsites successfully initiated to begin recruiting. 2 new clinical subsites initiated to begin recruiting in June 2017

Key Outcomes:

Publications: BMJ Open, vol. 6(6) pp. e012292, β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. Bhatt, SP; Connett, JE; Voelker, H; Lindberg, SM; Westfall, E; Wells, JM; Lazarus, SC; Criner, GJ; Dransfield, MT

PMID: 27267111 URL - http://www.ncbi.nlm.nih.gov/pubmed/27267111?dopt=Citation

Patents: N/A

Funding Obtained: N/A